Management of Gram-Negative Bloodstream Infections (GN-BSI) in Immunocompetent Adults

Questions? Page 970-GERM or the Antimicrobial Stewardship Evaluation Team (ASET) Pharmacist at 970-6666

General Guidance:

- Recommendations below are intended as a general guideline for management of GN-BSI to provide favorable clinical outcomes while minimizing unintended consequences. Patient-specific factors should influence decisions on agent, duration, and transition to oral therapy.
  - This criterion does not apply to immunocompromised hosts (eg, Solid organ recipients; hematopoietic cell transplant recipients; patients actively receiving chemotherapy; expected prolonged neutropenia with absolute neutrophil count <500 cells/mL; recent CD4 count <200 cells/mL; chronic high dose corticosteroids (prednisone ≥20 mg/day or equivalent) and/or immunomodulatory therapy).
- See **Figure** summarizing key steps in decision-making through diagnostic and therapeutic management of GN-BSI.

Step 1: Evaluate clinical factors indicating complicated versus uncomplicated GN-BSI (**Table 1**). Determine need for source control intervention and/or ID consult.

Table 1. Criteria for Uncomplicated vs Complicated GN-BSI:

	Uncomplicated	**Complicated (Recommend ID Consult)**
Source of Infection	Urinary tract infection (without prostatitis or renal abscess), intra-abdominal or biliary infection, pneumonia (without empyema/abscess or structural lung disease such as cystic fibrosis), SSTI, catheter-associated	Involvement of CNS, bone or joint infection, endocarditis/endovascular infection, implanted material (e.g. hardware, devices, grafts), liver abscess
Source Control	Yes (e.g., removal of infected catheters, near complete drainage of infected fluid collections, relief of urinary or biliary tract obstructions)	Source control not achieved
Clinical Factors	Clinically improving on current antimicrobial therapy within 72h of effective antibiotic treatment defined by: 1. Afebrile 2. Hemodynamic stability 3. Resolving or resolved leukocytosis	Defervescence or hemodynamic stability not achieved after 72 hours.

SSTI: Skin and soft tissue infection, CNS: central nervous system

Note: Pathogens with limited treatment options (e.g. *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Stenotrophomonas maltophilia)* including those with multidrug resistance may warrant ID consultation for treatment choice and duration decisions.

Step 2: Select empiric antibiotic(s) and (if indicated) document blood culture clearance

A. Empiric Therapy

1. Individual patient factors including severity of presentation (e.g., septic shock), previous antibiotic exposure and previous culture data should be reviewed and utilized to guide empiric therapy
2. In patients with suspected intra-abdominal source or mixed soft tissue infection, metronidazole should be added to ceftriaxone, cefepime, aztreonam or ciprofloxacin for anaerobic coverage. Piperacillin/tazobactam provides adequate coverage for obligate anaerobes as monotherapy.
3. Empiric antibiotic therapy recommendations based on initial speciation from rapid diagnostics can be found on Custom ID Rapid Diagnostics page.
4. Clinical pharmacists may dose adjust (increase or decrease) antibiotics based on patient renal function. Full policy guidance and renal dose adjustments are located on CustomID.

B. Repeat Blood Cultures: Repeat blood cultures to document clearance ONLY if at least ONE of the following are true:

1. Complicated GN-BSI (See **Table 1**)
2. Patients do NOT have appropriate clinical response within 72 hours of starting antibiotics (afebrile, hemodynamically stable, resolving leukocytosis)
3. Endovascular infection or endocarditis
4. Limited or no source control
5. Hemodialysis
6. Indwelling intravascular device (including cardiac devices)
7. Delayed (>24 hours from when initial blood culture drawn) appropriate antibiotic therapy

Step 3: Tailor antibiotic therapy and/or switch to appropriately dosed oral agent based on susceptibility data and clinical response.

C. Targeted Therapy: Adjust antibiotics based on antimicrobial susceptibility results to narrow spectrum agent (**Table 2**) UNLESS pathogen is known to have drug-resistance:

1. Extended-spectrum Beta-lactamase (ESBL)-producing: Enterobacterales that are intermediate or resistant to ceftriaxone are considered ESBL-producing and should be treated with a carbapenem (meropenem 500 mg IV q6h (0.5 hr) or ertapenem 1 g IV once daily). ID approval is required.
2. AmpC-producing: Patients with uncomplicated GN-BSI from ampC pathogens *Enterobacter cloacae*, *Klebsiella (Enterobacter) aerogenes*, or *Citrobacter freundii* can be treated with cefepime when cefepime susceptible and not cefepime resistant or susceptible dose-dependent. Due to the risk of inducible beta-lactamase production, ceftriaxone and piperacillin-tazobactam are NOT recommended for GN-BSI, even if reported as susceptible.

Table 2: De-escalating Antibiotic Therapy

IV (preference for narrowest-spectrum susceptible antibiotic)
Ampicillin 2g IV q4h^
Ampicillin/sulbactam 3g IV q6h
Cefazolin 2g IV q8h^
Ceftriaxone 2g IV q24h^

*See DUH CustomID for renal dose adjustments

^Addition of metronidazole required for anaerobic coverage

D. Transition to Oral Therapy Considerations:

1. Source control achieved
2. Patient clinically improved on effective intravenous antibiotics within 48-72h (e.g., afebrile, leukocytosis improving)
3. Patient has an intact and functional gastrointestinal tract
4. Culture data demonstrates susceptibility to an appropriately dosed oral antibiotic **(Table 3)**
5. Patients with GN-BSI due to ESBL- or AmpC-producing pathogens can be transitioned to oral fluoroquinolones or trimethoprim/sulfamethoxazole if they fulfill all other criteria above.

NOTE: The following oral agents should **NOT** be used for GN-BSI:

i. Cefdinir due to unfavorable pharmacokinetics and association with worse clinical outcomes.

ii. Agents with limited systemic absorption or low serum levels (eg, fosfomycin, nitrofurantoin, doxycycline).

Table 3: Suggested Oral Antibiotic Therapy (consult pharmacy for patient specific dosing recommendations and for patients with obesity)

Agent[1,2]	**Suggested Dosing**[3]
Amoxicillin	1000 mg PO TID
Amoxicillin/ clavulanic acid	875-1000 mg PO TID
Cephalexin^	1000 mg PO QID
Ciprofloxacin	500-750 mg PO BID
Levofloxacin	750 mg PO daily
Trimethoprim/sulfamethoxazole	5 mg/kg PO BID (eg, ~2 DS tablets q12h for a 70 kg patient)

[1]**Patient- and pathogen-specific factors should be considered when selecting an oral transition agent for gram-negative bacteremia**

[2]Alternative oral beta-lactam agents (*i.e.* cefuroxime 1g q12h, cefpodoxime 400mg q12h, and cefadroxil 1g q12h) are less preferred based on agent bioavailability, ability to achieve adequate serum concentrations, and/or limited clinical data. Use may be considered on a case-by-case basis in discussion with ID/ASET.

[3]Doses assume normal renal function. See DUH CustomID for renal dose adjustments

^Cefazolin susceptibility reported on urine culture does NOT predict susceptibility for GN-BSI due to use of different breakpoints. Use the cefazolin susceptibility from blood cultures to determine if oral cephalexin is active.

Step 4: Determine appropriate duration of therapy based on antibiotic agent, infection source, and route.

E. Duration of Therapy: 7 days of active therapy for uncomplicated GN-BSI

1. Uncomplicated GN-BSI should be treated with a 7-day total course of effective IV and/or oral therapy
2. For uncomplicated GN-BSI, day 1 is the first day of therapy on an antibiotic to which the pathogen was susceptible. For patients requiring source control interventions, day 1 is the day of source control or first day of effective therapy, whichever came last.
3. For patients with complicated GN-BSI, longer durations may be warranted, in agreement with existing indication-specific guidelines, documented blood clearance, and/or ID recommendation.
4. In patients requiring outpatient parenteral antibiotic therapy, please consult ID to determine treatment plan prior to the day of discharge.

Management of Gram-Negative Bloodstream Infections (GN-BSI) in Immunocompetent Adults

Questions? Page 970-GERM or the Antimicrobial Stewardship Evaluation Team (ASET) Pharmacist at 970-6666

References:

1. Canzoneri CN et al. Follow-up blood cultures in gram-negative bacteremia: Are they needed? *CID*. 2017;65(11):1776-9. doi: 10.1093/cid/cix648.
2. Kang CK et al. Can a routine follow-up blood culture be justified in *Klebsiella pneumoniae* bacteremia? A retrospective case-control study. *BMC Infect Dis*. 2013;13:365. doi: 10.1186/1471-2334-13-365.
3. Kutob LF et al. Effectiveness of oral antibiotics for definitive therapy of gram-negative bloodstream infections. *Int J Antimicrob Agents*. 2016. doi: 10.1016/j.ijantimicag.2016.07.013.
4. Rieger KL et al. Intravenous-only or intravenous transitioned to oral antimicrobials for *Enterobacteriaceae*-associated bacteremic urinary tract infections. *Pharmacotherapy*. 2017;37:1479-83.
5. Tamma PD et al. Association of 30-day mortality with oral step-down vs. continued intravenous therapy in patients hospitalized with *Enterobacteriaceae* bacteremia. *JAMA Intern Med*. 2019. doi: 10.1001/jamainternmed.2018.6226.
6. Mercuro NJ et al. Retrospective analysis comparing oral stepdown therapy for *Enterobacteriaceae* bloodstream infections: fluoroquinolones vs. B-lactams. *Int J Antimicrob Agents*. 2017. doi: 10.1016/j.ijantimicag.2017.12.007.
7. Gumbleton R et al. Treatment failure rates in patients receiving low versus high oral bioavailability antibiotics for gram-negative bacteremia. *J Am Coll Clin Pharm*. 2018;1:220.
8. Punjabi C et al. Oral fluoroquinolone or trimethoprim-sulfamethoxazole vs beta-lactams as step-down therapy for *Enterobacteriaceae* bacteremia: systemic review and meta-analysis. *OFID*. 2019;6(1). doi:10.1093/ofid/ofz364.
9. Al-Hasan MN et al. Transition from intravenous to oral antimicrobial therapy in patients with uncomplicated and complicated bloodstream infection. *Clin Microbiol Infect*. 2019. doi.10.1016/j.cmi.2019.05.012
10. Park TY et al. Early oral antibiotic switch compared with conventional intravenous antibiotic therapy for acute cholangitis with bacteremia. *Dig Dis Sci*. 2014;59:2790-6. doi: 10.1007/s10620-014-3233-0.
11. Sawyer RG, Claridge JA, Nathens AB, et al. Trial of short-course antimicrobial therapy for intraabdominal infection. N Engl J Med 2015; 372:1996–2005.
12. Mogle BT et al. Clinical considerations for oral beta-lactams as step-down therapy for *Enterobacteriaceae* bloodstream infections. *Expert Opin Pharmacother*. 2019;20:903-7
13. Chotiprasitsakul D et al. Comparing the outcomes of adults with *Enterobacteriaceae* bacteremia receiving short-course versus prolonged-course antibiotic therapy in a multicenter, propensity score-matched cohort. *CID*. 2018;66(2):172-7. doi:10.1093/cid/cix767.
14. Havey TC et al. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. *Crit Care*. 2011;15(6):R267. doi:10.1186/cc10545.
15. Nelson AN et al. Optimal duration of antimicrobial therapy for uncomplicated gram-negative bloodstream infections. *Infection*. 2017;45(5):613-20.
16. Yahav D et al. Seven versus fourteen days of antibiotic therapy for uncomplicated gram-negative bacteremia: A noninferiority randomized controlled trial. *CID*. 2018 Dec. doi:10.1093/cid/ciy1054.
17. Fabre V, Amoah J, Cosgrove SE, Tamma PD. Antibiotic therapy for Pseudomonas aeruginosa bloodstream infections: how long is long enough? Clin Infect Dis 2019; 69:2011–4.
18. Sutton JD, Stevens VW, Chang NN, et al. Oral β-lactam antibiotics vs fluoroquinolones or trimethoprim-sulfamethoxazole for definitive treatment of Enterobacterales bacteremia from a urine source. JAMA Netw Open 2020; 3:e2020166.
19. Von Dach E, Albrich WC, Brunel AS, et al. Effect of C-reactive protein-guided antibiotic treatment duration, 7-day treatment, or 14-day treatment on 30-day clinical failure rate in patients with uncomplicated gram-negative bacteremia: a randomized clinical trial. JAMA 2020; 323:2160–9.
20. Hojat LS, Bessesen MT, Huang M, et al. Effectiveness of shorter versus longer durations of therapy for common inpatient infections associated with bacteremia: a multicenter, propensity-weighted cohort study. Clin Infect Dis 2020; 71:3071–8.
21. Daneman N, Shore K, Pinto R, Fowler R. Antibiotic treatment duration for bloodstream infections in critically ill patients: a national survey of Canadian infectious diseases and critical care specialists. Int J Antimicrob Agents 2011; 38:480–5.
22. Grayson M, Crowe S, McCarthy J, Mills J, Mouton J, Norrby S. Kucers' the Use of Antibiotics. 6th ed. CRC Press; 2010.
23. Arancibia A, Guttmann J, González G, González C. Absorption and disposition kinetics of amoxicillin in normal human subjects. Antimicrob Agents Chemother 1980; 17:199–202.
24. De Velde F, de Winter BC, Koch BC, et al. ; COMBACTE-NET consortium. Non-linear absorption pharmacokinetics of amoxicillin: consequences for dosing regimens and clinical breakpoints. J Antimicrob Chemother 2016; 71:2909–17.
25. Cattrall JWS, Asín-Prieto E, Freeman J, Trocóniz IF, Kirby A. A pharmacokinetic-pharmacodynamic assessment of oral antibiotics for pyelonephritis. Eur J Clin Microbiol Infect Dis 2019; 38:2311–21.
26. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing M100. 31st ed. Wayne, PA. 2021.
27. Mitaka H, Gomez T, Lee YI, Perlman DC. Risk factors for positive follow-up blood cultures in gram-negative bacilli bacteremia: implications for selecting who needs follow-up blood cultures. Open Forum Infect Dis 2020; 7:XXX–XX.
28. Maskarinec SA, et al. Positive follow-up blood cultures identify high mortality risk among patients with gram-negative bacteraemia. Clin Microbiol Infect 2020; 26:904–10.
29. Kim H, et al. Bedside risk prediction for positive follow-up blood culture in Gram-negative bacilli bacteremia: for whom is follow-up blood culture useful? Infection. 2022 Jun;50(3):689-697. doi: 10.1007/s15010-021-01742-2. Epub 2022 Jan 21. PMID: 35060101.
30. Heil EL, et al. Optimizing the management of uncomplicated Gram-negative bloodstream infections: consensus guidance using a modified delphi process. OFID. 2021;8(10):1-7. doi.org/10.1093/ofid/ofab434
31. Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America Antimicrobial-Resistant Treatment Guidance: Gram-Negative Bacterial Infections. Infectious Diseases Society of America 2022; Version 1.1. Available at https://www.idsociety.org/practice-guideline/amr-guidance/. Accessed 21 August 2022.